Medical Device Sterilization Town Hall: Sterility Master files and Effective Use in Premarket Submissions
September 11, 2024

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello, everyone. Thanks for joining us for our eleventh Medical Device Sterilization Town Hall. This is Commander Kim Piermatteo of the United States Public Health Service, and I serve as the Education Program Administrator in the Division of Industry and Consumer Education within CDRH's-- or, sorry, within FDA's Center for Devices and Radiological Health, or CDRH. I'll be serving as the moderator for today's Town Hall.

The FDA is committed to reducing reliance on ethylene oxide sterilization use while ensuring the integrity of the supply chain so that patients and providers have continued access to the sterile devices they need. To meet this goal, FDA continues to take a multi-pronged approach, including regulatory flexibilities, supply chain analysis and mitigation, collaboration, innovation, and communication, including this series of town halls.

For today's Town Hall, we will begin with a segment of what we heard from you. Then our panelists will provide discussions on four topics. And then we will have our live question and answer segment where we look forward to hearing from you. If you have a comment or question for this last segment, please wait to raise your hand in Zoom to get into the queue until we transition to this specific part of today's Town Hall.

Now I'd like to share a few administrative items before I introduce and turn it over to today's panelists. First, please make sure you joined us through the Zoom app and not through a web browser to avoid technical issues. And second, trade press reporters are encouraged to consult with the CDRH trade press team at cdrhtradepress@fda.hhs.gov. And members of national media may consult with FDA's Office of Media Affairs at fdaoma@fda.hhs.gov.

I now have the pleasure of introducing today's panelists: CDR Scott Steffen, Senior Program Management Officer and EtO Incident Lead in the Division of All Hazards Preparedness and Response in the Office of Readiness and Response within CDRH's Office of Strategic Partnerships and Technology Innovation, or OST; Dr. Angel Soler-Garcia, Lead Microbiologist on the Incontinence and Female Urology Devices Team within the Office of Health Technology number three for Gastro, Renal, OB/GYN, General Hospital, and Urology Devices in the Office of Product Evaluation and Quality, or OPEQ; Dr. Ryan Ortega, Regulatory Advisor on the Regulatory Policy and Combination Products Staff within OPEQ; Matthew Beckwith, Lead Reviewer in the Office of Health Technology number two for Cardiovascular Devices within OPEQ.

Joining these panelists also is Christopher Dugard, Assistant Director in the Office of Health Technology number four for Surgical and Infection Control Devices in OPEQ; Dr. Mitali Patil, General Engineer in the Office of Health Technology number two for Cardiovascular Devices in OPEQ; and Dr. Anita Khatiwara, Biologist, also in the Office of Health Technology number two for Cardiovascular Devices in OPEQ.

Thank you all for joining us for our Town Hall today. I'll now turn it over to Scott to get us started.

CDR Scott Steffen: Thank you, Kim. And thank you all for joining us to our eleventh Sterilization Town Hall. Before we get started with our discussion today, I'd like to take the opportunity to discuss a couple of questions we received recently in our mailbox. Question one, could we have a webinar on the status of novel gaseous sterilants proposed in the last few years-- for example, supercritical carbon dioxide or nitrogen dioxide?

Answer. We've received interest in this topic from a number of sources. Please note that FDA has been involved in some initiatives, like Innovation Challenge 1, which has participants that are exploring alternate modalities, like supercritical CO2 and nitrogen dioxide. We talked about this innovation challenge in Town Hall 2, and instructions to locate this Town Hall information is provided at the end of this presentation.

As we've mentioned in the past, we're not experts in some of these alternate modalities. To learn more, we may consider reaching out to firms performing these sterilization modalities for their subject matter expertise. We are also expanding our own knowledge, including through our engagements with the innovation challenge participants. Another way we seek to learn more about alternate modalities is through our Experiential Learning Program, or ELP.

Firms are encouraged to participate in our ELP as another way to educate the Agency on evolving sterilization landscape. A link to our ELP page is also included on our resources slide at the end of this presentation. Once the FDA has sufficient information, we certainly consider this a potential topic for a future event.

Question two, we continue to receive additional inquiries regarding shelf life. Specifically, do I need to submit a new 510(k) to expand our new shelf life? Therefore, we wanted to ask or touch on this topic again. Answer. Section B4, page 27 of the FDA guidance document, Deciding When to Submit a 510(k) for a Change to an Existing Device, addresses this issue.

If the same method or protocol described in a previously cleared 510(k) is used to extend the shelf life, then generally, a new 510(k) is not needed. However, where methods or protocols that are not described in a previously cleared 510(k) are used to support shelf-life claims, submission of a new 510(k) is likely needed.

Our modification guidance mentioned above was discussed during Town Hall 4 on February 29, 2024, and instructions to access this information are available by following the town hall link on our medical device sterilization town hall series web page. Next slide, please.

We've shared this timeline previously. The information highlighted here is relevant to today's presentation and includes links to our master file pilot programs. As you may remember, we've mentioned master files a number of times in previous town halls. In Town Hall 2, we discussed how master files are intended to streamline regulatory processes for firms to make process changes. In Town Hall 4, we broke down the individual pilots from 2019 through 2023.

In today's town hall on medical device sterilization, we're going to zoom out and look at the big picture regarding master files. Our panel will focus on the four topics shown here. Topic one-- what is a master file, its purpose, and applicability? Topic two, master file versus sterility master file pilot similarities and

differences. Topic three, FDA expertise with the sterility master file pilot effective use in premarket submissions. Topic four, master file general guidelines and best practices, a reviewer perspective.

Note our panelists will mention several websites. Links will be included in the resources slide at the end of today's presentation. I think you'll find this to be a great and informative town hall. So let me pass it on to Angel to get this discussion started on topic one.

Angel Soler-Garcia: Thank you, Scott. Hi, everyone. I'm Angel Soler-Garcia. And today our first topic will focus specifically in discussing exactly what master files are, their objective, and how they can be applied. To further the discussion, Matthew and Anita will be helping us better understand master files. To start with, Anita, can you please explain exactly what master files are for us?

Anita Khatiwara: Thank you, Angel. A master file is the submission of information that allows FDA to confidentially review such information from a party who has not submitted or will not directly submit the information in a marketing submission, such as IDE, 510(k), and PMA or other device related submissions. Additionally, master files can be utilized for devices, biologics, drugs, food, and veterinary medicine.

Each type of master file has a separate web page, since the content and the use of the master file may vary among FDA centers. Today's presentation will focus on device master files and sterility master files submitted to CDRH.

Angel Soler-Garcia: Thank you, Anita, for describing what a master file is. To expand more on this topic, Matt, can you describe what master files can cover?

Matthew Beckwith: Sure, Angel. So device master files can cover just about anything we normally see in a premarket review. So general topics include, but, of course, are not limited to, facilities and manufacturing procedures and controls, specifications for chemicals or materials, sub-assemblies for a device, and even clinical study data. So it's pretty versatile.

Angel Soler-Garcia: Thank you. That's quite an array of topics that a master file can cover. Matt, I have a follow up question. Do you have any general examples of master files that you have commonly seen?

Matthew Beckwith: Sure, sure, yeah. So commonly in the past, we've had master files to support significant changes in packaging or device materials that impact many different manufacturers. These master files and their amendments included information such as descriptions and reasons for these changes in materials, detailed testing plans to address the changes, and complete testing protocols and reports based on those test plans.

So by including this type of information in a master file, these packaging or device material changes can be applied to many different devices that are impacted by the master file holder. So keep in mind that these individual sponsors that apply the master file to their products in the premarket submission, they usually require the necessary letter of authorization form from the master file holder for permission to reference the master file in their premarket submissions.

Angel Soler-Garcia: As Matt said, master file of this type can be applied to numerous devices that are impacted. Anita, can you describe the expectations of device manufacturers regarding to the application of a master file?

Anita Khatiwara: Sure, Angel. To support a change, we expect device manufacturers, as applicable, to reference the master file, conduct a risk analysis, implement their change control procedures, update their device master record, conduct appropriate qualifications, and document rationale for accepting the change.

Angel Soler-Garcia: Thank you, Matt and Anita. That was a great introduction about what is a master file. Its objective and applicability. Matthew will now we lead a discussion about stability master files. Matthew.

Matthew Beckwith: Thanks, Angel. So I have Chris Dugard and Ryan Ortega with me to provide a bit more insight into the similarities and differences between normal master device files and sterility master device pilot program. So Chris, can you please point out how the sterility master file pilot differs from a typical device master file?

Christopher Dugard: Hi, Matt. Thanks, yeah. I'd be glad to take that one. So there are no specific content requirements for a traditional device master file. However, a submission will not be accepted as a master file if it is not substantive in nature. Additionally, master files will typically include information that may be regarded as trade secret, or confidential, commercial, or financial information.

With a master file, the holder can allow sponsors to reference their master file when appropriately authorized, but can refrain from sharing the actual information in the master file with the sponsors. When a submission references a master file or amendment to a master file, the master file or amendment is reviewed based on what is referenced in the submission.

However, sterility master file is specific to sterilization considerations with clear content expectations, as described in the FR notices for these pilots. These sterility master files may encompass sterilization practices for devices across the offices in the FDA, and are therefore reviewed by all the different review offices. These sterility master files serve as a pilot to allow for certain regulatory flexibilities, for certain sterilization changes for approved or cleared devices, depending on the scope of the pilot you're choosing.

Matthew Beckwith: Awesome. Thank you, Chris. While we're at it, can you describe the amendment process for master files?

Christopher Dugard: I'd be happy to. So both standard and sterility master files can be amended, as they may need to be updated with new information. This information can include additional testing, additional applications of the information, or modifications of the product or products that are the subject of the submission.

For instance, for a sterility master file pilot, the master file holder may want to include other sterilization lines in the master file to increase capacity or include additional cycles. The master file holder can provide the validation data for those additional sterilization lines or cycles for FDA to review. Please note that for traditional device master files, while FDA will acknowledge the receipt of the amendments,

the amendments are not typically reviewed until they're referenced in a submission. Once referenced in a submission, FDA will then review both the submission and the amendment together.

Matthew Beckwith: Thanks for the detailed breakdown, Chris. A lot of sponsors get confused about the amendment process, so it's important to clear that up. Ryan, can you provide more details about how one may reference a master file or master file amendment?

Ryan Ortega: Yeah, Matt, I'm happy to provide some info there. I definitely would want folks to keep in mind that whenever referencing either a traditional device master file, a sterility master file in one of the pilots, or an amendment to either type of those master files in a submission, the manufacturer must receive authorization from the master file holder or from an authorized designated agent for that master file.

And so essentially, that authorization lets us know that the manufacturer has permission from the owner of the master file to reference it. However, the authorization is only for referencing the master file. That's an important point. It doesn't necessarily grant the client access to the information in the master file, but again, it informs us that the contents of the master file are pertinent to the review of the client's device submission.

So when the master file holders provide this letter of authorization directly to their client, they should inform the client that the original of the authorization letter should be included in the original copy of the client submission. So that's the actual submission for the device. Also, a copy of this letter should be placed in each subsequent copy of the device submission. Again, another note here that this authorization letter shouldn't be sent directly to CDRH for inclusion in the master file.

It should really be a part of the submission itself. And so essentially what this means is that if you do need to reference a master file in a submission, again, please include that authorization letter in the submission. Don't send it to us as kind of its own standalone document. And if you're interested, additional information on authorization to a master file can be found on our device master file website. And there is a link provided in the resources at the end of this presentation.

Matthew Beckwith: Awesome. Thanks, Ryan, for providing more insight on how to reference master file. I know it's a lot of information, but it's important to get this right as we apply these master files to a wide variety of different devices. Are there any other specific considerations for sterility master files?

Ryan Ortega: Yes, Matt, and I wholeheartedly agree with you with the importance of getting this right. And kind of in that spirit, there are some additional considerations, especially considering that the sterility master file pilots are technically separate pilot programs. And like we've been talking about a little bit, they are separate and distinct from how we've traditionally used device master files.

So to refresh everyone's memory, we have three sterility master file pilots, one for PMA devices that are making changes to ethylene oxide sterilization, one for PMA devices going from one radiation source to another, or potentially going from ethylene oxide to radiation, and one for 510(k) devices that are making a modality change away from ethylene oxide.

I'll start with a point about the two PMA sterility master file pilots, since these two are somewhat similar. In this case, the sterility master file holder should notify any PMA holders that have been

granted the right to reference their sterility master file pilot once that master file has been accepted into the pilot program.

And once that sterility master file has been accepted, FDA will consider permitting authorized PMA holders with devices that are in the scope of the accepted sterility master file to reference that sterility master file in post approval reports as an alternative to submitting information in a PMA supplement to support that sterility change. That's kind of the what's in it for me for the device manufacturer.

And more information about referencing sterility master files and post approval reports for PMA devices can be found in the procedures for PMA holders section in the federal register notices for those two pilots.

So moving on to the 510(k) sterility master file pilot, the procedures for 510(k) holders is a little bit different because that pilot is allowing for certain changes to be made without actually submitting a new 510(k). And so in this case, once a sterilization provider has proposed and FDA has accepted a master file into the pilot program, then 510(k) holders who are given right of reference for their devices that are in scope of the accepted master file, can then reference that master file in their internal documentation to support the sterilization change from fixed chamber ethylene oxide to whatever process is described in the accepted master file.

And this is instead of submitting a new 510(k). Like with the PMA sterility master file pilots, I would definitely encourage interested device manufacturers to check out the procedures for 510(k) holders, section of the Federal Register notice for the 510(k) focused pilot. And again, links to these FR notices are included in the resources slide at the end of the presentation.

Matthew Beckwith: Awesome. Thanks so much for letting us know about those provisions from the Federal Register Notice, Ryan. Now that we know a bit more about the differences between these two approaches, when do you think it would be more appropriate to use the sterility master pilot program instead of a typical device master file?

Christopher Dugard: Hi, Matt. This is Chris. I think I can take that one. I think that's a great question. So we think there are important opportunities to use the sterilization master pilot program to assist in supporting more efficient use of ethylene oxide and to support flexible changes in sterilization methods, like going from ethylene oxide to another modality.

For instance, it may be more beneficial to use a sterility master file when you're working with your sterilization provider to change from your previously validated ethylene oxide cycle to a newly validated ethylene oxide cycle that uses a lower concentration of the sterilant for a PMA device.

You may also consider using a radiation sterility master file when changing your sterilization modality from ethylene oxide to a radiation based modality, or using the 510(k) sterility master file pilot to change a 510(k) device from ethylene oxide to a method we might consider to be an established category B method.

Matthew Beckwith: Awesome. Thanks so much, Chris. And thank you both for the robust discussion. I hope we're able to convey that this pilot program can be a great tool for manufacturers to consider as

they attempt to modify sterilization in a wide array of products. Now, I'll turn it over to Angel again for the next discussion topic.

Angel Soler-Garcia: Thank you, Matt. And now we will move on to discuss our specific experiences with the effective use of sterility file pilots in premarket submissions. As was discussed before, on the panel, we have Anita, Mitali, Chris, and Ryan. And to start this discussion, we would like to share the current sterility master file pilots. First, Anita, can you let us know why ethylene oxide is so prevalent as a sterilization modality?

Anita Khatiwara: Sure, Angel, I'll be glad to. So ethylene oxide sterilization is an important sterilization method that manufacturers widely used to keep medical devices safe. For many medical devices, sterilization with ethylene oxide gas may be the only method for effective sterilization without damaging the device during the sterilization process, especially for certain types of materials, layered packaging, or devices with hard-to-reach places.

About 50% of all sterile medical devices in the United States are sterilized with ethylene oxide. FDA reviews all premarket submissions to determine if the sterility information is in accordance with FDA recognized and internationally agreed upon voluntary consensus standards. For ethylene oxide in particular, there are standards in place to ensure that the level of residuals, namely ethylene oxide and ethylene chlorohydrin on medical devices, are within safe limits.

Angel Soler-Garcia: Thank you, Anita, for describing you know why ethylene oxide has such a widespread use as a device sterilant. But before we talk more about our experiences with the sterility master files in premarket review, Ryan, can you please provide a little background about why we initiated these pilots?

Ryan Ortega: Yeah, definitely, Angel, and that's some pretty important context. I think, as we generally all know, recently the EPA has been looking to reduce the impact of ethylene oxide emissions. And for our part, we want to ensure that we're supporting responsible use of this sterilant, and also supporting the use of alternative sterilants.

So we develop things like our sterility innovation challenges and the sterilization master file pilot programs to help ensure that patients have access to safe, sterile, medical devices and also to encourage new, innovative ways to sterilize devices or make sterilization changes. We implemented the innovation challenges really just a few months before our first sterility master file pilot. And I think our work on the challenges helped us to realize that developing the master file pilots could help us reduce some of the regulatory review that's needed to make changes to some of these more optimized ethylene oxide cycles for PMA devices.

We started with that first ethylene oxide pilot for PMA devices and later expanded to a 510(k) focus pilot, and then our radiation pilot for PMA devices. And that was based on some of the lessons learned throughout the process.

Also, these pilot programs are really intended to help avoid potential device shortages while still ensuring that we're maintaining our ongoing commitment to safety. We really think that this program and all of our work in this area will help bolster the medical device supply chain by supporting agility and flexibility in sterilization changes.

Angel Soler-Garcia: Thank you, Ryan, for providing some background for how our sterility master file pilots fit into our current efforts to help reduce EO emissions. To spawn more regarding to the sterility master pilots, Mitali, can you please provide more details about specific sterility master file pilots that we have in place?

Mitali Patil: Sure, Angel. We currently have three sterility master file pilots, which you can learn more about on our FDA website page titled Sterilization for Medical Devices. First, we have the ethylene oxide sterilization master file pilot program, which is a voluntary program intended to allow companies that sterilize single use medical devices using fixed chamber ethylene oxide to submit a master file when making certain changes between sterilization processes and facilities that reduce the amount of ethylene oxide concentrations on medical devices. This program is intended for PMA holders of class 3 medical devices.

Second, we have the radiation sterilization master file pilot program, once again, for PMA holders. And it's for companies that sterilize single use PMA approved devices using radiation. This program is intended to help contract sterilizers and medical device manufacturers make changes to or advance alternative ways to sterilize approved medical devices, including changing radiation sources in a least burdensome regulatory approach.

Both of the previous master file pilot programs applied to PMA devices. But we do have a third master file pilot program in place, which is for 510(k) devices. The 510(k) ethylene oxide sterility change master file pilot program is intended to help with changes to a cleared medical device's sterilization method from a fixed ethylene oxide sterilization cycle to the sterilization method described in the master file.

Angel Soler-Garcia: Thank you, Mitali, for providing an overview of the sterility master file pilots. Furthermore, Chris, can you please provide a bit more details about how the current submissions under these pilot programs are beneficial for both FDA and industry?

Christopher Dugard: Yes, I definitely can, Angel, thank you. Typically, we see these sterility master file pilots being used to support changes in sterility across several similar devices at once. For instance, there are sterility master files that support the use of a reduced ethylene oxide concentration in a sterilization cycle that is applicable to product families relevant to the master file.

By providing the validation data and rationale to support why the sterilization cycle is applicable to all the products in the scope of that master file, the master file holder can then apply the sterilization change, the sterilization cycle change, to all the products in one single master file without having to submit supplements for each device. For instance, for PMA holders, a master file, or the relevant amendment to that master file, may be referenced in an annual report, rather than submitting a separate supplement for the sterilization cycle change described in the master file.

This is just one example of how sterility master file pilots can be utilized to streamline specific changes in the sterilization process in accordance with the general guidelines outlined in the Federal Register notices for each pilot program.

Angel Soler-Garcia: Thank you, Chris, for providing this sample. And thank you to all the panel members for this thoughtful discussion. Now I will turn it over to Ryan for the next discussion topic.

Ryan Ortega: Yeah, thanks, Angel. And thanks for leading the discussion about the sterility master file pilot programs. So now, I'd like to discuss some general guidelines for master files and the sterility master file pilot programs, as well as some best practices based on some of our reviewer experiences. So for this part of the discussion, our panel has Anita, Mitali, and Angel. And Angel, I think I'll start with you. Can you kick us off by telling us a little bit about where to find more information about some of the guidelines for master files?

Angel Soler-Garcia: Thank you, Ryan, for that question. And yes, the FDA has multiple resources online that outline the general guidelines for master files. This includes the 1987 guidance document. And we have a specific, was mentioned before, an FDA website for the standard master file.

For the sterility master file pilot programs, they are more specific, they are more specific requirements outline. And those are contained in the specific federal registers. Please note that these resources are listed in slides 13 and 14 of today's presentation.

Ryan Ortega: Yeah, thanks, Angel, for drawing people's attention to those resources. And now I think I'll open it up. Does anyone on the panel have any initial thoughts regarding some best practices for master files that have come up, I guess, as part of FDA review of master files?

Anita Khatiwara: Thank you, Ryan. This is Anita. I can go first. There are certain considerations to take into account when preparing to submit an original master file for review. I would like to start by emphasizing the importance of working with FDA via Pre-Submission to discuss the proposal for a master file, including an overview of the testing and validation that will be provided in the master file.

This is particularly useful for sterility master file pilots, but could also be helpful for a traditional device master files if there are specific questions.

Mitali Patil: This is Mitali. I agree with Anita's points and would like to add that when preparing master files for submissions, please note that all facilities need to be registered with the FDA. So this includes manufacturing facilities, testing facilities, and sterilization facilities. In particular, sterilization facilities should be compliant with FDA guidelines and regulations and should have an acceptable inspectional history.

Angel Soler-Garcia: This is Angel. I will also to add that anybody should ensure that for the sterility master file pilots in particular, that you are complying with all the requirements outlined the specific Federal Register that I mentioned earlier. And that included in the resources outlining the slides 13 and 14 of this presentation.

Ryan Ortega: Thank you all for sharing some of those considerations for master files. I'll note that these seem to be best practices prior to submitting a master file. Do you have any thoughts for best practices for master files after they've been acknowledged by FDA?

Angel Soler-Garcia: That's a good point, Ryan. When referencing the master file in a submission, especially a master file with numerous amendments, it will be beneficial to reference the specific amendment and, if applicable, the page numbers with the relevant testing validation associated with the device or devices that are in the scope of the submission.

Anita Khatiwara: Yeah, this is Anita. I agree with Angel's point. And additionally, I would like to highlight what Chris mentioned earlier, that when referencing a master file that is not a sterility master file, or when referencing an amendment to any master file, it's important to note that we do acknowledge the receipt of master files or amendments, but that does not mean we have reviewed them. Typically, the review of the master file and amendments occur when they are referenced in the submission and are appropriately authorized to do so.

Mitali Patil: This is Mitali. To add on to Angel and Anita's comments, it's also important to note that when we review the master file or amendments, we may encounter some issues with the information present in the master file. As the contents of a master file are confidential, these issues or concerns may be discussed interactively with the master file holder only.

If they are not resolved interactively, we may need to issue deficiencies to the master file holder only. In that scenario, the sponsor who referenced the master file will only be informed in a deficiency that there is an issue with the master file, but will not be provided any specific information about the issues that are prevalent in the master file.

If the master file holder was working with a testing, sterilization, or manufacturing facility and items were found deficient regarding a specific facility, then the master file holder will have to work with that facility to resolve the deficiency.

Ryan Ortega: Again, thank you, all three of you. This was a great discussion about some best practices and considerations for master files. Thank you for leveraging your experience and your subject matter expertise for this really thoughtful discussion. And so I think that concludes our panel discussion for each of the four topics. So I will turn it back over to Scott to start bringing us home.

Scott Steffen: Thank you, Ryan. So the next two slides include the resources mentioned earlier in the presentation, along with the full URLs that you can access after the presentation.

Today's presentation or panel discussion centered around master files and their utility as an alternate mechanism to communicate medical device information outside of marketing applications. We provided brief insight into the standard and sterility focused master files, including the following-- content and expectations of the different master file types, current sterility master files and their impact in premarket submissions, resources to help determine if a master file can be a way to communicate your medical device information to the FDA. Next slide, please.

Before we open the discussion, I'm excited to announce our next town hall on October 9, where we plan to host at least one short topic discussion, including premarket change control plans or PCCPs. Our panel will also engage in an interactive discussion and live Q&A on topics identified by the audience and topics provided prior to the event via our medicaldevicesterilization@fda.hhs.gov mailbox. The information about the town hall series can be found at the link here. Now let me turn it back over to Kim.

CDR Kim Piermatteo: Thanks, Scott. And thank you, everyone, for some great panel discussions. So now we will transition to our question-and-answer segment. Before we get started, I'm going to go over how we will manage this segment. So to ask a question or provide a comment, please select the Raise Hand icon in Zoom, which should appear in the bottom of your Zoom screen. I'll announce your name and give

you permission to talk. When prompted in Zoom, please select the blue button to unmute your line. Please identify yourself and your organization and then ask your question or provide your comment. If you have a question, please remember to limit yourself to asking one question only and try to keep it as short as possible. After you ask your question or provide a comment, please lower your hand. And then if you have another question or comment, please raise your hand again to get back into the queue and I will call on you as time permits.

So as we-- excuse me-- as we wait to receive some of your questions or comments today, I'd like to start us off with a few questions to our panelists that we've received. And the first question I'll direct towards Matt. So, Matt, the question I have for you is, are there any specific content requirements for a traditional device master file?

Matthew Beckwith: Yeah, so device master files can be submitted for various functions. So there's no specific content requirements for master file. However, a submission will not be accepted as a master file if it's not substantive in nature or if it doesn't contain information that may be regarded as either a trade secret or confidential information, whether that be commercial or financial.

Please also note that there are some specific documentation requirements, as well. A master file submission must include a cover letter, preferably on a company letterhead signed by a responsible official. This letter should not only identify the submission as a master file, but also include a contact person or designated agent. All master files are unique, though, and if you're interested in submitting one for the first time, I recommend starting with the Pre-Sub to smooth out the process.

CDR Kim Piermatteo: Thanks, Matt. OK our next question, I want to direct that to Mitali. Mitali, the question is, if our master file involves the use of a sterilization facility in any capacity, are there any considerations to keep in mind regarding documentation related to the sterilization facility?

Mitali Patil: Thanks for bringing up that question. It is of utmost importance to identify the sterilization facility, its location address, the facility registration number, and inspectional history. This information is needed to meet current FDA expectations regarding sterilization facility registration. Please note, as a final rule, effective October 11 in 2012, to support the implementation of the Food and Drug Administration Amendments Act of 2007, which was enacted on September 27, 2007, FDA updated its expectations for sterilization site registration to state that all contract manufacturers and contract sterilizers are required to register their establishments and list their devices. This final rule is codified in the Code of Federal Regulations, title 21, section 807.21. And we've included a link regarding registration and listing requirements in the resources slide that Scott referred to earlier with more information.

Additionally, the master file holder should be aware of the facility's inspectional history, operational status, and history of compliance with applicable regulations prior to the master file submission, as FDA will ascertain these details upon receipt of a master file if facility with official action indicated, or an OAI classification does not qualify for sterility master file pilot program. Also of note, manufacturers must submit a PMA supplement if there is a change of sterilization facility identified in its original PMA submission for sterilizing the subject device. For a cleared 510(k) device, we recommend that you please work with the specific FDA division to determine how to appropriately file for a change in sterilization facility.

CDR Kim Piermatteo: Thanks, Mitali. Alright, so we have two more questions I wanted to get through before we take our first live question. The next question, Chris, I wanted to direct this one to you. The question is, I have an innovative sterilization modality. How am I able to move this to an established Category B modality so that I may consider a master file pilot submission?

Christopher Dugard: That is a great question. So the biggest concern the Agency has when we're considering new modalities is familiarity with the said modality, including safety and effectiveness. So the gold standard to support that would be a recognized consensus standard. However, there are other ways to increase our familiarity with the modality, such as use of that modality in a cleared 510(k) or a granted De Novo for a health care sterilizer, using that modality, or reviews where we've been able to look at full validation reports, such as PMA reviews.

CDR Kim Piermatteo: Thanks, Chris. So for our next previously submitted question, I'm going to come to Ryan. Ryan, that question is, can you clarify if firms with a master file are required to register and list with the FDA that master file?

Ryan Ortega: Yep, sure. It's a fairly straightforward answer, but it is a really important clarification. Firms with a master file are not required to register or list the master file.

CDR Kim Piermatteo: Thanks, Ryan. Alright, we will now take our first question. That's coming from Jessica. Jessica, I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

Jessica, I have unmuted your line. Are you-- there you go.

Jessica Singelais: Yes, sorry. Hi, I'm Jessica from Novo Source, LLC. I was wondering if you could provide any feedback on manufacturers being able to submit changes as special 510(k)s. Obviously, with the novel, I would expect it to need to be a traditional. But if you're moving from one chemical sterilant to another, do you see any pathway for being able to review that as a special?

CDR Kim Piermatteo: Thanks, Jessica, for that question. I'm going to open it up to our panelists, if anyone wants to jump in.

Ryan Ortega: I can maybe get us started and then see if anybody on one of the review teams has some perspective. I think for a Special 510(k)s, it might be more kind of case specific, right. I think it really could depend on how different the new method is from the old method, what kind of category it falls in within the context of that 510(k) sterility guidance.

I think it might be one of those things where a quick check with the review division for that specific device might be able to provide a little bit of direction. They might be able to tell a device manufacturer well, if that might be a little more complicated than you think, you could do a Q-Sub, or they might be able to tell you a little bit more directly what might be an option. Or they may clarify that because of that type of change, it would really need a traditional.

But again, I do think it comes down to the specifics about what's the old modality, what's the new modality, and some specifics about the device itself.

Christopher Dugard: Yeah, and this is Chris. Just to add a little bit to that, it's 100% correct. And to add a little bit more flavor to it, really what it comes down to is what's impacting safety and efficacy of the device. And for that I refer to our modifications to 510(k) cleared devices that may need future submissions. We've got a guidance on that we've linked previously and other town halls on our resource pages. Really, what it comes down to is if the modality change is going to impact the safety and efficacy of the device, it's likely not appropriate for a special.

And while that usually translates to us sticking with established A or established B modalities, when we're considering a special, we can't rule out other modalities. If you could justify that a change is not impacting the safety and efficacy of the device, then there may be a potential conversation to be had around that.

Matthew Beckwith: Yeah, I'll also chime in that we have a special 510(k) guidance, as well. And that has a pretty nifty flow chart, which can help you make these decisions, as well.

Jessica Singelais: Yes, thank you. I am familiar with those. I appreciate your answer. I do think there is an argument to be made for that. And yeah, I appreciate it.

CDR Kim Piermatteo: Thanks, Jessica, for your question. And thank you, Ryan, Chris, and Matt. Alright, our next question is coming from Tina. Tina, I have unmuted your line. Please unmute yourself and ask your question.

Tina O'Brien: Hi, this is Tina O'Brien from Aroa Biosurgery. We've been recently advised that our current EO facility-- it's the third party-- is going to completely change out their chamber and reconfigure some of their space. And I know that this is a little off topic from the master files. But just wondering what the Agency's view on that is? I would consider that a significant change that would probably need some notification to the Agency for our 510(k) devices. But I'm also curious if that's something that we could encourage this EO site to prepare a master file to help cover the gap for us.

CDR Kim Piermatteo: Thanks, Tina, for your question. I'm going to open it up to one of our panelists. I'm not sure-- this more premarket, but—

CDR Scott Steffen: So Kim, I can give this a try to start us off and see if other people can chime in. So I think it really depends on the kinds of change that you're talking about and what's being involved, and also the type of the device. I don't know if you mentioned if it was a class 2 device, or a class 3 device. I would always defer to the MOD's guidance if that is a considerate that you want to bring up.

And also, are you going from what category-- what category of method you're going to the other category of method. Those are things that you might want to consider, as well. The other thing, too, is that voluntarily, if there's an issue and you want to bring it to our attention, you can voluntarily submit a 506(j) notification if you feel that might have some sort of pending issue with supply.

But those are some of the initial thoughts that I had there. And let me see if the other people on the team might have other things they would like to add to that.

Christopher Dugard: Thank you, Scott. This is Chris again. I can add a little bit. Really, if the question is, would it be useful to encourage this facility to submit a master file? And I believe the answer would be

yes, especially if they plan to continue to make changes. Continuously making changes like this would be burdensome on any PMA device that is utilizing that facility. And that burden would be alleviated if the sterilizer were to have an accepted master file in place. So we would already know what their change process looks like and how they're validating it.

Tina O'Brien: Would that be the same for a 510(k) device?

Christopher Dugard: Again, it really depends on the device and the appropriate master file pathway and the modalities you're using. Because as we've described-- yes, yeah.

Tina O'Brien: I was just going to say, so it's an EO facility. And we're not changing modality. They're completely rejigging the entire facility and the chamber. So obviously we're going to have to revalidate all of our products. And just trying to get our heads around what that regulatory burden looks like from an FDA perspective for us. But I'm happy to take offline and go through another route to keep-- because I know that this is off topic.

Christopher Dugard: Yeah, it is a great question. And I do encourage a Pre-Submission if you have specific questions around this device and the proposed changes.

Tina O'Brien: OK, thank you.

CDR Kim Piermatteo: Thank you, Tina. Our next question is coming from Penny. Penny, I have unmuted your line. Please unmute yourself and ask your question.

Penny Houston: Hello, this is Penny Houston from Bass Martin Consulting, LLC. I just wanted to, first of all, commend the FDA today for your webinar. It's been very informative. And actually, the question before mine just got asked. I was going to ask, you mentioned that to utilize the Pre-Sub program for questions regarding the sterilization master files. And I was just going to ask, did you have any successful types of examples under which to utilize that method?

CDR Kim Piermatteo: Thanks, Penny. So I know that's a very specific question. So I'm going to ask any of our panelists if they want to comment on what Penny's asking.

Ryan Ortega: I think while we can't maybe talk specifics about companies' Pre-Subs, I can say that we have been seeing a lot of sterility information, sterility questions, and Pre-Subs. Personally, from my reviewer time and now in my current role, I've seen a lot of utility and having some of those discussions of in the context of a Pre-Sub.

I really like them because it's a chance to provide some early input, some early thoughts to a Pre-Sub submitter, which is often the device manufacturer, about what they're planning or proposing. If they have very well thought out specific questions, we could potentially address challenges even before they pop up and give them some early considerations.

And personally, from my perspective, it's a good learning opportunity for us, too, particularly if we're having Pre-Sub discussions around alternative modalities or potentially new or innovative sterilization activities or approaches. So I think it's just been a really useful mechanism for us and hopefully for industry, too, both the manufacturers and the sterilizers, for having some of these conversations, both

about alternative modalities, but also to make them master file submission process or really any submission process a little bit more smooth, a little bit-- have a little bit clearer expectations, too.

Penny Houston: Wonderful. Thank you for your answer.

CDR Kim Piermatteo: Thanks, Penny. Thank you, Ryan. So if you have a question for our panelists, please raise your hand in Zoom. I'd like to come back to Ryan for a previously submitted question that we've got. So, Ryan, that question is, can parametric release be utilized in a master file submission?

Ryan Ortega: Yeah, sure. Good question. I know that parametric release is often on a lot of people's minds with respect to sterility. And we haven't ruled it out either in a traditional device faster file or one of the sterility master file pilots.

In practice, I do think it's important to emphasize that if you're implementing parametric release, there really is this need for sufficient historical evidence over control of that process. Right. That's a critical thing for understanding that meeting those parameters is achieving sterilization in a controlled, repeatable fashion.

So one thing that we do recommend is that you discuss your specific situation with us prior to submission of a master file if you're going to include parametric release, for example. I think that, again, could help make the process more smooth, make sure that everybody understands the expectations. And we can answer any questions that you might have.

CDR Kim Piermatteo: Thanks, Ryan. I'm going to come to Chris. Chris, I want to ask another question that we received that I think is going to benefit this group. So the question is, you mentioned that there are sterilization master file pilot programs that are currently in place. Is it possible to join these master file programs?

Christopher Dugard: Thanks. Yeah, so please note that for two of the sterilization master file pilot programs, they're intended for PMA holders only. And one is intended for 510(k) cleared medical devices. So FDA's announced these master file pilot programs via Federal Register notices, which provide a point of contact, some background information regarding the master file pilot program, and requirements and procedures necessary for participation in that program.

FDA recommends that you reach out to your respective review office or review team for additional information or for links to the federal registers if you have trouble finding them. In addition, we shared information about these pilot programs during Town Halls 2 and 4. Materials for specific town hall events can be found using instructions provided in this presentation. Thank you.

CDR Kim Piermatteo: Thanks, Chris. Again, if anyone has any questions, please raise your hand. If not, I'm going to go to Anita for another question. And then we will move to close today's town hall. So, Anita, the question is, is it possible to amend a master file?

Anita Khatiwara: Thank you, Kim. This is a great question. FDA understands that the information may be needed to be updated in a master file due to additional testing, additional application of the master file information, or modification of the product that is the subject of the master file. Therefore, it is permissible to amend or add to a master file. However, please note that when referencing a master file

with multiple amendments in a subsequent submission, please provide the specific amendment you wish to reference and whether any previous submissions referencing the amendment have been approved.

CDR Kim Piermatteo: Thanks, Anita. That's very helpful. And thank you to everyone for your questions. And thank you again to all of our panelists for engaging with everyone today and providing responses to the questions. I'd now like to turn it back over to Scott to provide some closing remarks.

CDR Scott Steffen: Yeah, thank you, Kim. And thank you all for joining us to today's town hall and our panelists discussion about master files and for sharing your questions and comments via email during the live Q&A.

Here are some high-level takeaways that I got from the town hall today. We discussed the differences between master files and master file pilots. We gave a perspective on the use and best practices of those master files, and then we had a really robust discussion on questions ranging from specific content requirements, documentation related to sterilizers, moving a sterilization method, moving of a sterilization method classification or category to be considered in a master file, the idea of registration and listing regarding master files, feedback on what manufacturers that are submitting changes, and if it should be a special 510(k), but also talking about how we one could leverage the 510(k), the special 510(k) guidance and the Q-Sub program, the use of 506(j) notifications, changes to sterilizers in general, what master file information should be included when pertaining to a new modality, and the idea of joining the master file program, amending master files. And, lastly, we were talking specifically about the idea of parametric release.

Again, we thank you all for this robust discussion. These topics, they're always really helpful for us to hear and how it makes us understand and move the content forward with subsequent town halls. So thanks again for attending. And now I'll turn it back over to Kim to close us out. Kim.

CDR Kim Piermatteo: Thanks, Scott. So for me, printable slides of today's presentation are currently available on the Events page for this town Hall and in CDRH Learn. And we will post a recording of today's town hall and a transcript in the next few weeks. That will be posted to CDRH Learn and the Events page. And a screenshot of where you can find these materials is on this slide under the CDRH Learn image.

If you have additional questions or comments about today's town hall, as well as if you have a comment or question for a future town hall, please email medicaldevicesterilization@fda.hhs.gov. And additionally, you can find a listing of all of our upcoming medical device sterilization town halls and other webinars on our CDRH events page at www.fda.gov/CDRHevents.

And lastly, as Scott mentioned, just another reminder that our next sterilization town hall will be held on October 9, from 2:00 to 3:00 PM Eastern time. We hope you're able to join us again in October.

Thanks again for joining us today. This concludes our town hall.

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